

Crigler-Najjar syndrome

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[Abstract](#)

[Keywords](#)

[Disease and synonyms](#)

[Excluded diseases](#)

[Incidence](#)

[Clinical description](#)

[Methods of biological diagnosis](#)

[Genetic counseling](#)

[Prenatal diagnosis](#)

[Comments and unresolved questions](#)

[References](#)

Abstract

Crigler-Najjar syndrome is a very rare disease (incidence around 1/1,000,000 births) associated with a complete hepatic deficit of bilirubin glucuronosyltransferase activity. The disease becomes apparent during the neonatal period by early, intense jaundice due to unconjugated bilirubin. The physical examination is normal; biological analyses detect only severe unconjugated hyperbilirubinemia. Type I Crigler-Najjar syndrome is unaffected by phenobarbital induction therapy, where as 3 weeks of phenobarbital can lower bilirubinemia by 60-70% in type II Crigler-Najjar syndrome. The definitive diagnosis is based on the demonstration of the enzymatic deficiency in the liver (hepatic biopsy after 3 months of age). Treatment of type II Crigler-Najjar syndrome consists of daily phenobarbital, while that of type I relies on phototherapy (initially at the hospital and then at home) for 10-12 hours per day. The only effective treatment for type I is liver transplantation. Children with Crigler-Najjar syndrome type I or II (the latter to a lesser degree except before the diagnosis has been obtained or during intercurrent episodes) have a permanent risk of developing neurological complications as a consequence of the neurotoxicity of unconjugated bilirubin. The molecular bases of types I and II are known. The mutations are numerous. Molecular biology, the only way to obtain a prenatal diagnosis of type I, confirmed the autosomal recessive inheritance of Crigler-Najjar syndrome, even though some exceptions have been noted in type II.

Keywords

uridine diphosphate-glucuronosyl transferase deficiency, unconjugated hyperbilirubinemia, intense jaundice, phenobarbital, phototherapy, liver transplantation.

Disease and synonyms

Crigler-Najjar syndrome is linked to a permanent deficit of uridine diphosphate-glucuronosyltransferase (UDPGT; EC 2.4.1.17) activity. This disease is also described under the

name of hereditary unconjugated hyperbilirubinemia.

Excluded diseases

By definition, Crigler-Najjar syndrome is a disease affecting bilirubin-glucuronide formation. Thus, all diseases whose metabolic substrate is

downstream from this reaction are excluded, for example, Rotor and Dubin-Johnson syndromes. Although Gilbert's syndrome shares the same enzyme deficiency as Crigler-Najjar syndrome and the same gene is responsible, in the former, the enzyme deficit is only partial and the molecular bases within the same gene differ from those in the latter. Diagnostic criteria/Definition The permanent deficit in UDPGT (EC 2.4.1.17) is responsible for Crigler-Najjar syndrome. This enzyme catalyzes bilirubin conjugation to diglucuronic acid leading to the formation of mono- and diglucuroconjugate derivatives. The biological definition of the syndrome relies on the existence of unconjugated hyperbilirubinemia alone. This definition means that all other causes of unconjugated hyperbilirubinemia have been eliminated, primarily hemolysis and neonatal infections. Moreover, other than hyperbilirubinemia, all other biological parameters of hepatic function are normal.

Incidence

Crigler-Najjar syndrome, either type I or type II, is an extremely rare entity, whose incidence is estimated at 1:1.000.000 births.

Clinical description

Crigler-Najjar syndrome is manifested, as of the first hours of life, by the appearance of severe jaundice due to unconjugated bilirubin, leading, in almost all cases, to emergency exchange transfusion(s). The infant is then subjected to phototherapy for 12 hours/day. The clinical distinction between Crigler-Najjar syndrome types I and II is based on the efficacy of phenobarbital therapy: type I hyperbilirubinemia is unchanged by this induction treatment, whereas phenobarbital induces a rapid decline of the plasma bilirubin concentration in children with type II Crigler-Najjar syndrome. Phenobarbital is considered effective when bilirubinemia decreases by two-thirds after 2-3 weeks of treatment. The efficacy of this induction therapy maintains the bilirubin concentration below the neurotoxicity threshold. The clinical distinction between types I and II has been known since 1969 and is still relevant. This difference is capital, since, at present, the only treatment for type I Crigler-Najjar syndrome is liver transplantation. Indeed, the risk of neurological involvement is permanent in patients with type I Crigler-Najjar syndrome, despite chronic daily phototherapy. Kernicterus can occur at any age, even in adolescence or adulthood, especially when phototherapy is (ill advisedly) stopped, or during intercurrent infectious episodes, fasting or stress. The neurological complications represent the true gravity of type I Crigler-Najjar syndrome. In contrast, long-term phenobarbital therapy for type II Crigler-Najjar syndrome is effective,

reliable and well tolerated by children who grow to adulthood. However, the extreme rarity of the disease makes it difficult to evaluate the long-term prognosis, even though it is generally known that phototherapy is well tolerated, other than possible cutaneous lesions secondary to treatment-related skin fragility.

Methods of biological diagnosis

The diagnosis is suggested when severe unconjugated hyperbilirubinemia appears early in life. However, other potential causes of this hyperbilirubinemia must be eliminated, particularly hemolytic syndromes. Then, analysis (by high-pressure liquid chromatography) of the glucuroconjugated derivatives of bilirubin in serum can be informative, even though its interpretation is difficult in very young infants. Analysis of these derivatives in bile can also be contributive but is more difficult to achieve because of the necessity for duodenal intubation to collect bile under the best technical conditions. Finally, when the diagnosis of Crigler-Najjar syndrome seems probable, phenobarbital induction therapy should be tested to evaluate the sensitivity of the disease to this treatment so as to distinguish clinically between types I and II. In any case, the definitive diagnosis of type I Crigler-Najjar syndrome is based on the demonstration of a total, non-inducible deficit of liver UDPGT activity. To conduct this test, a needle biopsy of the liver should be performed when the infant reaches 3 months (in fact, UDPGT activity undergoes maturation and the 'definitive' values are not achieved until the 3rd month of life). Molecular biology studies cannot differentiate, based on the type of mutation, between Crigler-Najjar syndrome types I and II. However, certain mutations already identified in patients whose enzymatic activities have been measured, on the one hand, the existence of founder effects for Crigler-Najjar syndrome type I on the other, enable case-by-case confirmation of the diagnosis of type I. Otherwise, techniques can be used to examine in vitro expression and thus to study the functional consequences of the responsible mutation(s).

Genetic counseling

Two human complementary DNA (cDNA) coding for two isoforms of UDPGT have been cloned. They are the products of a single large complex of genes located at the telomeric extremity of the long arm of chromosome 2. This large locus covers at least 110 kb. It comprises 4 consecutive exons (exons 2-5), regrouped at the 3' end coding for the C-terminal regions which are identical in all the UDPGT isoforms. At least 10 different exon-1 types are located upstream from these 4 common exons. Exon 1, which codes for the N-terminal region corresponding to each UDPGT isoform, carries

a promoter at its 5' end that regulates the expression of the multiple products of this large locus. Thus, the resulting different mRNA are the products of the alternative use of different promoters combined with alternative splicing phenomena. The molecular pathology of the type I Crigler-Najjar syndrome has been clearly described. It is a genetically heterogeneous disease and numerous mutations have been reported. Founder effect have been recognized in certain geographic regions (Portugal, Sicily, Tunisia). The molecular pathology of type II Crigler-Najjar syndrome has also been described. Type I Crigler-Najjar syndrome is autosomal recessive and carries a 25% risk of a second child being born with the disease. Type II Crigler-Najjar syndrome also seems to be autosomal recessive and thus carries the same risk of 25%; the difference in this case is that therapeutic possibilities exist. In contrast, several observations based on molecular results have suggested that autosomal dominant inheritance is possible: molecular biology can be particularly useful in guiding the genetic counseling of these rare families.

Prenatal diagnosis

The severity of type I Crigler-Najjar syndrome justifies, in many cases, proposing prenatal diagnosis. The activity of UDPGT is not detectable in the fetal tissues usually used for prenatal diagnosis (trophoblast, amniocytes, fetal blood). The genetic heterogeneity of the disease, in addition to the existence of compound heterozygotes, makes a direct approach difficult. Moreover, the UDPGT locus shows little polymorphism and the use of an indirect approach by restriction fragment length polymorphism or microsatellite polymorphism is also difficult. Thus, at present, prenatal diagnosis can only be proposed case by case, provided that the family could have been studied beforehand, particularly the index case whose genotype must have been precisely determined.

Comments and unresolved questions

Treatment of type I Crigler-Najjar syndrome remains cumbersome and the perpetual threat of neurological complications weighs on these children until a transplant can be performed. This intervention is not without risks and the penury of grafts is more-and-more evident. Although we must remain prudent, type I Crigler-Najjar syndrome would seem to be a good candidate for gene therapy because it is a severe disease that is difficult to treatment, but which would be cured if the total enzyme deficit could be transformed into a partial deficiency, since 2-3% of UDPGT activity suffices to lead a normal life. Numerous studies have been started in animals to test different approaches to durably transferring the desired gene into the liver or other tissues. In addition, other research

strategies are being explored to obtain drugs able to inhibit bilirubin production. Finally, other therapeutic avenues have also been advanced and/or attempted: hepatocyte transplantation, chimeric oligonucleotides, etc.

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